PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	25.01.2006
Applicant's or agent's file reference: PC26158A	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB2004/003668	08.11.2004	20.11.2003

Applicant
WARNER-LAMBERT COMPANY LLC

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

   The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

   Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

   For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

   The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Krage, D Tel. +49 89 2399-7530

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PC26158A	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/IB2004/003668	International filing date *(day/month/year)* 08.11.2004	Priority date *(day/month/year)* 20.11.2003
International Patent Classification (IPC) or national classification and IPC C07D213/74, A61K31/4965		
Applicant WARNER-LAMBERT COMPANY LLC		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 4 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the International application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☒	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
17.12.2004	25.01.2006
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Zellner, A Telephone No. +49 89 2399-8078

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/IB2004/003668

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages	
1-35	as originally filed
Claims, Numbers	
1-14	filed with telefax on 14.04.2005
Drawings, Sheets	
1/1	as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-14
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-14
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-14
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

1. The following documents (D) are referred to in this communication; the numbering will be adhered to in the rest of the procedure:

   D1: DE 22 30 392 A1 (CASSELLA FARBWERKE MAINKUR A.-G.) 31 January 1974
   D2: EP-A1-0 293 744 (BASF A.-G., FED. REP. GER.) 7 December 1988
   D3: WO 03/002544 A (BRISTOL-MYERS SQUIBB COMPANY; PHARMACOPEIA, INC; AHMED, GULZAR; METZGE) 9 January 2003
   D4: US 2003/186984 A1 (ACKERMANN, JEAN ET AL) 2 October 2003
   D5: WO 2004/058174 A (BAYER PHARMACEUTICALS CORPORATION; CANTIN, LOUIS-DAVID; CHOI, SOONGYU;) 15 July 2004
   D6: EP-A-1 122 242 (YAMANOUCHI PHARMACEUTICAL CO. LTD) 8 August 2001

2. The present application relates to pyridine derivatives and their use as androgen modulators.

3. The amendments filed with letter dated 14.04.2005 are in accordance with the requirements of Art. 34(2)(b) PCT.

item **V**

4. Novelty (Art. 33(2) PCT)

   The compounds disclosed in Documents D1-D4 are not considered falling within the scope of amended claim 1 due to the restriction of substituent R^1. The requirements of Art. 33(2) PCT are thus fulfilled.

5. Inventive step (Art. 33(3) PCT)

   Doucment D6 relates to compounds with anti-androgen action (see the abstract). The presently claimed compounds differ from compound 1-23 (table 7, p. 32 of D6) in an additional substituent R^1 and in that the N-atom does not form part of a cyclic structure. It would appear that the provision of compounds according to present claim 1 cannot be considered obvious for the skilled person when starting from the disclosure of D6 in order to solve the technical problem of providing further compounds useful as androgen

modulators. The claimed subject-matter which can thus be considered based on an inventive step as well. The application meets the requirements of Art. 33(3) PCT.

6. Industrial applicability (Art. 33(4) PCT)

Can be acknowledged for claims 1-14.

item **VI**

7. Document D5 was published after the priority date of the present application but before its international filing date. Its content would be considered as forming part of the state of the art if the priority of the present application was found to be invalid. When entering the regional european phase the document will also be considered for the question of novelty even if the presently claimed priority is valid. Examples 310-312 of D5 do not fall within the scope of amended claim 1 due to the amendment of the definition for R^1.

item **VII**

8. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the cited documents is not mentioned in the description, nor are these documents identified therein.

item **VIII**

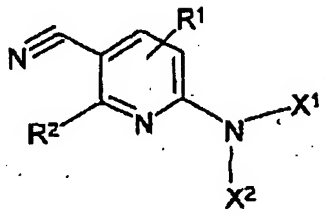
9. The expression "prodrug" does not have a precise meaning in the art and is thus not considered suitable to define subject-matter. Claim1 is thus not considered clear within the meaning of Art. 6 PCT.

10. Claims 9 and 10 are not acceptable under Art. 6 PCT. The therapeutic application is either not defined at all (claim 9) or functionally defined by a mecanism of action (claim 10) which does not allow any practical application in the form of a defined, real treatment of a pathological condition (disease).

CLAIMS

What is claimed is:

1. A compound of the formula:



and the pharmaceutically acceptable salts, hydrates, and prodrugs thereof, wherein;

a) R^1 is represented by (C_1-C_2)alkyl, substituted with one or more halogens, or (C_1-C_2)alkoxy, substituted with one or more halogens,

b) R^2 is represented by hydrogen or halogen,

c) X^1 and X^2 are each independently represented by

i) (C_1-C_{12})alkyl, optionally substituted,

ii) (C_2-C_{12})alkenyl, optionally substituted,

iii) (C_2-C_{12})alkynyl, optionally substituted,

iv) (C_3-C_{10})cycloalkyl, optionally substituted,

v) (C_3-C_{10})cycloalkyl(C_1-C_8)alkyl, in which the alkyl and cycloalkyl moieties may each be optionally substituted,

vi) (C_6-C_{10})aryl, optionally substituted,

vii) (C_6-C_{10})aryl(C_1-C_6)alkyl, in which both the alkyl and aryl moieties may be optionally substituted,

viii) $-(CH_2)_q-CH_2-ZH$, in which Z is S or O and q is an integer from 1-11,

ix) $-(CH_2)_n-Y-(CH_2)_p-CH_3$, in which Y is O or S, n is an integer from 1 to 4, and p is an integer from 1 to 4,

x) $-[CH_2]_m-C(O)R^3$, in which m is an integer selected from 1 to 8 and R^3 is represented by hydrogen, (C_1-C_{12})alkyl, (C_6-C_{10})aryl, or (C_6-C_{10})aryl(C_1-C_6)alkyl, in which both the alkyl and aryl moieties may be optionally substituted,

xi) $-[CH_2]_m-C(O)-O-R^4$, in which m is as defined above and R^4 is represented by hydrogen, (C_1-C_{12})alkyl, (C_6-C_{10})aryl, or

$(C_8$-$C_{10})$aryl$(C_1$-$C_6)$alkyl, in which the alkyl and aryl moieties may be optionally substituted,

xii) -$[CH_2]$m-C(O)-NR^5R^6 in which m is as described above, and R^5 and R^6 are each independently represented by hydrogen, $(C_1$-$C_{12})$alkyl, $(C_6$-$C_{10})$aryl, or $(C_6$-$C_{10})$aryl$(C_1$-$C_6)$alkyl, in which the alkyl and aryl moieties may each be optionally substituted,

i) heteroaryl, optionally substituted,

ii) heteroaryl$(C_1$-$C_6)$alkyl, in which the heteroaryl and alkyl moieties may each be optionally substituted,

iii) heterocyclic, optionally substituted, or,

iv) heterocyclic$(C_1$-$C_6)$alkyl, in which the alkyl and heterocyclic moieties may each be optionally substituted.

2. A compound according to claim 1 in which R^1 is represented by trifluomethyl.

3. A compound according to any one of claim s 1- or 2 in which said trifluoromethyl is located at the 4-position of the pyridine ring.

4. A compound according to anyone of claims 1-3 in which R^2 is hydrogen.

5. A compound according to anyone of claims 1-4 in which X^1 is $(C_1$-C12)alkyl and X2 is (C6-C10)aryl(C1-C6)alkyl.

6. A compound according to anyone of claims 1-5 in which X^1 and X^2 are each $(C_1$-$C_{12})$alkyl

7. A compound according to anyone of claims 1-6 in which X^1 is $(C_1$-$C_{12})$alkyl and X 2 is (C3-C10)cycloalkyl(C1-C6)alkyl.

8. A compound according to claim 1 selected from the group consisting of (R)-(+)- 6-[Methyl-(1-Phenyl-ethyl)-amino]-4-trifluoromethyl-nicotinonitrile,

(R)-(+)-2-Chloro-6-[methyl-(1-phenyl-ethyl)-amino]-4-trifluoromethyl-nicotinonitrile,

6-[methyl-(1-phenyl-ethyl)-amino]-4-trifluoromethyl-nicotinonitrile,
6-[methyl-(1-phenyl-ethyl)-amino]-4-trifluoromethoxy-nicotinonitrile,
6-[methyl-(1-(4-fluorophenyl)-ethyl)-amino]-4-trifluoromethyl-nicotinonitrile,
6-[methyl-(1-(3-hydroxyphenyl)-ethyl)-amino]-4-trifluoromethyl-nicotinonitrile,
6-[butyl(1-(3-hydroxyphenyl)-ethyl)-amino]-4-trifluoromethoxy-nicotinonitrile,
6-dipropylamino-4-trifluoromethyl-nicotinonitrile,
2-chloro-6-dimethylamino-4-trifluoromethyl-nicotinonitrile,
6-(hexyl-octyl-amino)-4-trifluoromethyl-nicotinonitrile,
6-(sec-butyl-methyl-amino)-4-trifluoromethyl-nicotinonitrile,
6-[butyl-(2-hydroxy-ethyl)-amino]-4-trifluoromethyl-nicotinonitrile,
6-(butyl-methyl-amino)-4-trifluoromethyl-nicotinonitrile,
6-(benzyl-methyl-amino)-4-trifluoromethyl-nicotinonitrile,
6-(cyclohexyl-propyl-amino)-4-trifluoromethyl-nicotinonitrile,
6-(cyclopropylmethyl-propyl-amino)-4-trifluoromethyl-nicotinonitrile,
6-(sec-butyl-methyl-amino)-2-chloro-4-trifluoromethyl-nicotinonitrile,
6-Dipropylamino-2-chloro-4-trifluoromethyl-nicotinonitrile,
6-(propyl-methyl-amino)-2-chloro-4-trifluoromethyl-nicotinonitrile, and,
6-(Butyl-methyl-amino)-2-chloro-4-trifluoromethyl-nicotinonitrile.

9. Use of a compound according to anyone of Claims 1-8 in the manufacture of medicament.

10. Use of a compound according to anyone of Claims 1-8 in the manufacture of a medicament for inhibiting activation of the androgen receptor.

11. A pharmaceutical composition comprising a compound according to any one of Claims 1-8 in admixture with 1, or more, pharmaceutically acceptable excipients.

12. A topical pharmaceutical formulation comprising a compound according to anyone of Claims 1-8 in admixture with 1, or more, pharmaceutically acceptable excipients suitable for dermal application.

13. An article of manufacture comprising a compound according to any one of Claims 1-8 packaged for retail distribution which advises a consumer how to utilize the compound to alleviate a condition selected from the group consisting of acne, alopecia, and oily skin.

14. Use of a compound according to any one of claims 1-8 in the manufacture of a medicament for alleviating a condition selected from the group consisting of hormone dependent cancers, benign hyperplasia of the prostate, acne, hirsutism, excess sebum, alopecia, premenstrual syndrome, lung cancer, precocious puberty, osteoporosis, hypogonadism, age-related decrease in muscle mass, and anemia.